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ROLE OF VITAMIN D AND DISORDERS OF ITS METABOLISM IN THE PATHOGENESIS OF BRONCHIAL ASTHMA

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БРОНХИАЛ АСТМА ПАТОГЕНЕЗИДА D ВИТАМИНИ ВА УНИНГ МЕТАБОЛИЗМИ БУЗИЛИШИНИНГ РОЛИ

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РОЛЬ ВИТАМИНА D И НАРУШЕНИЙ ЕГО МЕТАБОЛИЗМА В ПАТОГЕНЕЗЕ БРОНХИАЛЬНОЙ АСТМЫ

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Резюме. *Бугунги кунда, замонавий тиббиётнинг профилактика ва даволашда эришилган муҳим ютуқларга қарамай, болалар ва ўсмирларда ёмон кечувчи бронхиал астма билан касалланиш ҳолатлари кўплигича қолмоқда. Бронхиал астмани ўрганиш муаммосининг долзарблиги, биринчи навбатда, у иш фаолиятини пасайтириши, уйқу сифатини бузиши, айниқса тунги астма хуружлари сабабли, болалар ва ўсмирларнинг ҳаёт сифатини пасайтириши туфайлидир. Шу муносабат билан, ушбу мақола болаларда бронхиал астмада Д витамини етишмовчилиги ва унинг метаболизми бузилишининг мумкин бўлган роли ҳақида маълумот беради. Д витамини калтсий алмашинувига таъсири билан бир қаторда гормонлар ишлаб чиқаришни тартибга солади, ҳужайра пролиферациясига, дифференцсиатсиясига таъсир қилади, шунингдек, яққол иммуномодулятор таъсирга эга.*

Калит сўзлар: *Д витамини, болалар, бронхиал астма, етишмовчилик*

Abstract. *Today, there continues to be a significant number of cases of poorly controlled bronchial asthma in children and adolescents, despite the significant achievements of modern medicine in its prevention and treatment. The relevance of the problem of studying bronchial asthma is primarily due to the fact that it reduces performance, disrupts the quality of sleep, including due to nocturnal asthma attacks, reducing the quality of life of children and adolescents. In this connection, this article provides data on the possible role of vitamin D deficiency and disorders of its metabolism in bronchial asthma in children. Vitamin D, along with its effect on calcium metabolism, also regulates the production of hormones, affects cell proliferation, differentiation, and also has a pronounced immunomodulatory effect.*

Key words: *vitamin D, children, bronchial asthma, deficiency.*

Over the past two decades, there has been a significant revision and expansion of ideas about the role of vitamin D in the body [3,5].

The study of the metabolic system of vitamin D and its effect on the body is one of the current topics in modern healthcare. The interest in vitamin D in the scientific community is extremely high. Both the prevalence of deficiency of this vitamin and various aspects of its effect on the human body are being studied. Vitamin D is a common name that does not fully reflect the versatility of the roles of this substance. Recent studies have proven that vitamin D is a prehormone, one of the metabolome molecules that has a powerful effect on the genome, and vitamin D receptors (VDR) are located in a variety of organs and tissues. The effect of vitamin D is superior to that of all other vitamins. However, the function of vitamin D is possible only if the entire chain of vitamin transformations is completed and the effect of calcitriol on VDR [3,11].

Vitamin D is a group of unique biologically active substances involved in the regulation of a fairly large number of metabolic processes and the development of the child as a whole. Despite the fact that its amount in the human body is extremely small, its biological role is very multifaceted: synthesis of steroid hormones, regulation of calcium metabolism, participation in osteogenesis, etc. [2,4]. The main source of vitamin D in the body is endogenous synthesis, which occurs in the skin under the influence of ultraviolet radiation, resulting in the formation of vitamin D_3 (cholecalciferol) from 7-dehydrocholesterol. Only vitamin D_2 (ergocalciferol) enters the body with food, but its amount is extremely small [7,8].

Currently, the issues of the range of vitamin D content in serum, which can be considered normal, and the selection of the dose of vitamin D for its subsidization are actively discussed. Serum 25(OH)D levels between 30 and 100 ng /ml (75–250 nmol/l) appear physiologically reasonable. Vitamin D deficiency is one of the causes of the development of most diseases of civilization. The role of pediatricians in providing children with vitamin D and preventing the consequences of its deficiency is very great [1,12,13].

Unfortunately, there are currently no precise reference values for plasma vitamin D concentrations in newborns, which makes it difficult to diagnose deficiency and interpret research results, since only physiological indicators in adults are available [2,5,16].

In recent years, the interest of a number of researchers has increased in the possible role of vitamin D and disorders of its metabolism in the pathogenesis of bronchial asthma and obstructive pulmonary disease.

It has been established that vitamin D deficiency is quite common in both premature and full-term infants, which is associated with a high risk of developing respiratory diseases such as bronchial asthma, bronchiolitis and frequent infections of the respiratory system [8,12,22,23]. Vitamin D deficiency also has a negative effect on the development of the lungs and blood vessels of the pulmonary circulation, immune modulation, and may become one of the factors contributing to the development of neonatal sepsis [5,17]. Further research in this area is extremely important, since the effect of vitamin D deficiency on the newborn's body is undeniable, and its timely detection is of great clinical importance [8,18].

In recent years, the interest of a number of researchers has increased in the possible role of vitamin D and disorders of its metabolism in the pathogenesis of certain pulmonary diseases (asthma, chronic obstructive pulmonary disease, tuberculosis, cystic fibrosis, interstitial lung diseases) [19]. It is interesting to note that rickets is 2.5 times more common in children with chronic bronchitis. At the same time, it has been noted that the risk of chronic bronchitis is 10 times higher with severe rickets. Similar data are presented by Kunssaki (2011). There is evidence of the ability of $1,25(OH)2D_3$ to suppress the synthesis of immunoglobulins by B lymphocytes, inhibit the synthesis of IL-2 by T lymphocytes, and the effector function of T and B lymphocytes. Of particular importance may be the ability of $1,25(OH)D_3$ to inhibit the synthesis of Th-1 type cytokines (IL-2, IFNγ) and monocyte cytokine IL -12, which stimulates the synthesis of IFNγ by Th-1 lymphocytes (Dimeloe S., et al., 2010). A number of clinical studies have demonstrated a reduced risk of developing asthma, bronchoobstructive syndrome or recurrent episodes of wheezing in children under the age of three to five years born to mothers who took sufficient amounts of vitamin D during pregnancy [15,21].

Interest in vitamin D in bronchial asthma is due to its non-calcemic effects realized through VDR receptors located on the surface of immune cells, in particular macrophages and fibroblasts. In chronic inflammation, macrophages are antigen-presenting cells in type I immunological reactions according to Coombs and effector cells directly involved in inflammation in type IV inflammation [1,2].

The role of vitamin D in the pathogenesis of chronic inflammation in bronchial asthma is the object of study by many authors. Existing reviews of meta-analyses suggest an association between low serum vitamin D levels and an increased risk of developing AD, atopic dermatitis and high levels of total IgE and suggest possible ways to correct its level in children [14,20].

It is assumed that one of the mechanisms of the effect of vitamin D on allergic inflammation is an increase in the level of T-regulatory cells and a slowdown in the transformation of B cells into plasma cells, which can probably regulate the synthesis of IgE. At the same time, calciferol metabolites suppress excessive activation of macrophages and natural killer cells, which increases their survival, thereby reducing the risk of complications [1,3,6,10].

Masalsky S.S., et al., (2018) analyzed the frequency of detection of vitamin D3 deficiency in patients with bronchial asthma depending on the severity and number of exacerbations. The results of the work showed widespread D deficiency in patients with asthma, and the situation worsened in proportion to the severity of the disease and the number of exacerbations. The genomic polytopic effect of vitamin D on cell metabolism increases the proportion of patients with comorbid pathology, especially obesity. From the results of the study, the authors state that insolation in mild cases of bronchial asthma allows one to obtain a significant increase in the serum concentration of vitamin D and move from deficiency to deficiency of calciferol, but not to reach its optimal level. Moderate bronchial asthma has consistently

low levels of vitamin D throughout the year and is less susceptible to natural seasonal correction, which may be due to the peculiarities of 25-hydroxycalciferol metabolism during chronic inflammation. The authors take into account that GINA does not include vitamin D3 in the treatment algorithm for bronchial asthma, but given the total shortage of this important component, they consider it advisable to allocate patients with low vitamin D concentrations to a risk group for frequent exacerbations and prescribe cholecalciferol to correct the deficiency state.

As British scientists have shown, insufficient concentration of vitamin D may be the cause of a more severe course of bronchial asthma in children. The study examined the relationship between serum vitamin D (25(OH)D_3) concentrations and the clinical course of asthma in 86 children (mean age 11.7 years). Bronchial biopsies were taken from children with severe asthma. The results of the study showed that in children with severe resistant form of bronchial asthma, the level of vitamin D in the blood was significantly lower, the clinical picture of the disease was more pronounced, and there was a more significant decrease in pulmonary function compared to children with moderate asthma. Microscopy of bronchial tissue samples showed an increase in the number of smooth myocytes in the submucosal layer of the bronchi. According to the researchers, the data obtained suggest that low vitamin D levels in children with severe resistant asthma contribute to an increase in the mass of smooth muscle cells of the airways, which aggravates the course of bronchial asthma [13].

An interesting study was conducted by Li et al., analyzing the relationship of vitamin D status with pulmonary function and serum IgE concentrations in 435 Chinese people over 18 years of age with new-onset asthma. Vitamin D deficiency was reported in 88.9% of cases. After adjusting for age, sex, body mass index, smoking, season of blood collection, and duration of asthma symptoms, the authors found significant positive associations between 25(OH)D concentration, forced expiratory volume per second, and forced expiratory volume per second/forced vital capacity. However, no significant relationship was found between 25(OH)D levels and IgE concentrations [15].

The effect of vitamin D_3 on obesity occurs through the activation of genes responsible for activating the synthesis of proteins that bind insulin-like growth factor. With a lack of 1,25(OH)2D, glucose tolerance is impaired and adipogenesis is enhanced; on the other hand, calcitriol is able to stimulate the synthesis of activated peroxisome proliferator receptor m-δ, which enhances cholesterol utilization, realizing anti-atherosclerotic effects [3,4]. A second possible mechanism of action of vitamin D to improve asthma control is to reduce the number of infection-induced attacks. Analysis of the prevalence of vitamin D deficiency and morbidity indicates a more frequent occurrence of low calciferol levels in frequently ill children. There is evidence of a decrease in the incidence of acute respiratory viral infections, chronic tonsillitis and adenoiditis after therapy with vitamin D_3 due to the activation of the Th1 response and an increase in the level of neutrophil cathelicidins. Reducing the burden of viral infections directly reduces the number of exacerbations per year, especially in childhood [5,9].

Specifically E.A. McGinn et al. (2020) established a relationship between the level of vitamin D in the blood plasma of newborns and early adverse outcomes of hypoxic-ischemic encephalopathy according to magnetic resonance imaging of the brain. They demonstrated that when high doses of vitamin D were prescribed, the duration of mechanical ventilation in newborns during the first week of life was significantly reduced.

Fomin S.A. et al. (2021) in newborn children of St. Petersburg born in the autumn-winter-spring period, they found a significant decrease in the concentration of calcifedol relative to the age norm. The most pronounced deficiency of calcifedol turned out to be characteristic of children with severe congenital malformations requiring long-term treatment in the intensive care unit.

Thus, recent studies highlight the role of vitamin D and its receptors in the regulation of certain genes that are involved in inflammation, cell proliferation and differentiation, as well as in the functioning of the immune system. It is likely that compensation for vitamin D deficiency may help prevent or reduce structural changes in airway smooth muscle cells, which in turn will help relieve asthma symptoms and improve lung function.

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Резюме. *На сегодняшний день продолжает отмечаться значительное количество случаев плохо контролируемого течения бронхиальной астмы у детей и подростков, несмотря на значительные достижения современной медицины в ее профилактике и лечении. Актуальность проблемы изучения бронхиальной астмы в первую очередь обусловлена тем, что она снижает работоспособность, нарушает качество сна, в том числе из-за ночных приступов удушья, снижая качество жизни детей и подростков. В связи с чем, в данной статье приведены данные о возможной роли дефицита витамина D и нарушений его метаболизма при бронхиальной астме у детей. Витамин D наряду с влиянием на кальциевый обмен, также регулирует выработку гормонов, влияет на клеточную пролиферацию, дифференцировку, а также обладает выраженным иммуномодулирующим действием.*

Ключевые слова: *витамин D, дети, бронхиальная астма, дефицит.*